INTERVIEW SUMMARY

On November 15, 2006, Applicant's representative, Eric S. Furman, Ph.D., conducted an **in person** interview with Examiner Louise Humphrey, Ph.D., Primary Examiner Jeffrey Parkin, Ph.D.; and Supervisor Bruce Campbell. The parties discussed possible claim amendments in light of the rejections and art of record. No agreement was reached.

REMARKS

Applicants have canceled pending Claims 26-45 without prejudice or disclaimer and now present new Claims 46-70. The newly added claims find support throughout the specification and the claims as originally filed, for example at pages 2-4, 8-9, 11-16, 20-21, 32, 37, 40-43, 45-46, and 47-53. Accordingly, no new matter has been introduced by these amendments.

Interview of November 15, 2006

Applicants thank the Examiner, Primary Examiner Parkin and Supervisory Examiner Campbell for the courteous personal interview held on November 15, 2006 and the helpful comments made therein. Although an agreement was not reached, Applicants believe that the discussion of the case and prior art substantially moved prosecution forward.

Non-Statutory Double Patenting

The Examiner has provisionally rejected Claims 26-31 and 35 as allegedly being obvious over Claims 3, 8-11, 17, and 24 of U.S. Patent Application Serial No. 10/913,754. Co-pending U.S. Patent Application Nos. 11/411,294 and 11/411,454 also contain related subject matter. In an effort to expedite prosecution, Applicants submit herewith a Terminal Disclaimer that disclaims any patent term that extends beyond U.S. Patent Application Nos. 10/913,754, 11/411,294, or 11/411,454. Accordingly, Applicants respectfully submit that any Non-Statutory Double Patenting issues concerning these applications or patents that issue therefrom have been addressed.

35 USC § 103 - Obviousness

The Examiner has rejected Claims 26-31 and 35 under 35 USC § 103(a) as being obvious over Wang (WO 99/66957) in view of Galili et al. (1996). The Examiner asserts that it is obvious to one of skill in the art to modify the fragment of CD4 receptor provided by Wang by incorporation of the Gal epitope, as suggested by Galili et al., and that one of skill in the art would be motivated to do so to enhance presentation by APC of the CD4-ligand to specific helper T cell clones. The Examiner asserts that there would be a reasonable expectation of

success because the CD4 receptor contains oligosaccharides at two asparagine residues and Galili et al. provide various approaches to incorporate the Gal epitope on virion and subviral vaccines.

Galili et al. describe the preparation of an immunogenic composition that comprises an influenza virus linked to the Gal epitope (i.e., gal α (1,3) gal β). Galili et al. state:

> The HA molecule of the influenza virus has seven asparagine (N)-linked carbohydrate chains, which can serve as core structures for the synthesis of α-galactosyl epitopes. Virions expressing this carbohydrate epitope were obtained by propagation of the virus in bovine and canine cells which have α1,3GT. *(See column 1, last paragraph of page 322).*

Galili et al. later state:

> Our previous studies have indicated that when a virus is propagated in cells which are capable of synthesizing the α-galactosyl epitope (i.e. cells containing α1,3GT) then α-galactosyl epitopes are likely to be present on a portion of the N-linked carbohydrate chains of the envelope glycoproteins. *(See column 1, first paragraph of page 324).*

In discussing the difference in the amount of Gal epitope incorporated onto the virus produced from canine cells, as compared to bovine cells, Galili state:

> The lower amount of α-galactosyl epitopes present on PR8MDCK virus, compared to PR8MDBK virus may possibly be due to a lower activity of the cellular α1,3GT. *(See column 1, paragraph 1 of page 325).*

Galili et al. also state:

> The number of such epitopes per virion may vary depending on the activity of he α1,3 GT in the Golgi apparatus, the ability of this enzyme to compete with other glycosyltransferases in the same compartment (e.g., sialyltransferase) for capping the N-acetyllactosamine residues with a terminal sugar, and the length of time the carbohydrate chain is accessible within the Golgi apparatus to α 1,3 GT activity. The number of these epitopes may be increased to the extent that theoretically most of the carbohydrate chains on the virion will have the α-galactosyl epitope. *(See column 1, paragraph 2 on page 326).*

Finally, Galili et al. conclude:

> This study suggests that anti-gal may enhance the immune response to inactivated virus vaccines, if α-galactosyl epitopes are present on the virion or on the subviral vaccine. *(See column 1, paragraph 2 on page 326).*

Galili et al., demonstrate that cellular incorporation of the Gal epitope at multiple sites on a very large platform (a virion with seven sites for incorporation of the Gal epitope) is effective to enhance an immune response to the virus but that the technique is unpredictable and depends on the cell type used. Figure 3, for example, shows a reduced incorporation of Gal epitope on virus made in canine cells as compared to bovine cells.

Galili et al., also motivate one of skill in the art to incorporate as many epitopes as possible onto the virion or viral particles. In particular, Galili et al. describe ways to boost the incorporation of the Gal epitope by using recombinant α1,3GT and UDP-Gal provided that the carbohydrate chains on the viral glycoproteins contain *N*-acetyllactosamine. *(See page 326).*

Galili et al., however, do not describe, suggest, or motivate one to synthetically conjugate the Gal epitope on virions nor do they describe, suggest, or motivate one to incorporate the Gal epitope by any means on peptides. In particular, they do not describe, suggest, or motivate one to incorporate the Gal epitope on peptides corresponding to regions of the CD4 receptor that interact with HIV. There is no indication in Galili et al., that a technique that worked unpredictably with virions could be applied with any measure of success to peptides. There is no teaching as to how one would express the peptides in cells so as to incorporate the Gal epitope, for example. There is also no disclosure that describes how one would incorporate the Gal epitope to a peptide using a recombinant α1,3 GT. Galili et al. do not contemplate the addition of the Gal epitope to peptides and one of skill in the art reviewing the Galili reference would not come to realize Gal epitope conjugated peptides in the absence of Applicants disclosure. Given the unpredictability of incorporation of the Gal epitope in a virion with seven available sites for Gal epitope incorporation, one of skill in the art would not be motivated to apply the teachings of Galili et al., to generate peptides that contain a Gal epitope. Contrary to the Examiner's

assertion, there is no indication that the asparagine residues on the CD4 HIV binding region are available for incorporation of the Gal epitope or that the techniques described in Galili et al., would be effective at incorporating the Gal epitope on these residues or any other peptide. Further, one of skill in the art would not be motivated to apply the teachings of Galili et al., to the CD4 HIV binding region because the two asparagine residues that the Examiner states are available residues for incorporation reside within the CD4 HIV binding region itself, the domain to which one would want to generate antibodies and such incorporation would likely destroy the immunogenicity of the region rather than enhance immunogenicity. Additionally, one of skill in the art would not be motivated to synthetically conjugate the Gal epitope to a peptide, given the disclosure in Galili et al., because synthetic conjugation is an inefficient process for adding Gal epitopes at multiple sites, it is expensive, the yield is low, and Galili et al's teaching motivates one to add as many Gal epitopes as possible so as to improve immunogenicity.

Wang describes the preparation of peptide immunogens that comprise a promiscuous artificial Th epitope joined to a target antigenic site (e.g., immunosilent self-antigens) so as to generate a strong T helper cell-mediated response with the production of a high level of antibodies directed against the target antigenic site. (*See Field of the Invention).* Example 5 describes the preparation of one such peptide antigen that utilizes a modified CDR2-like domain of human CD4, wherein cysteine residues were incorporated at the N and C terminus so as to generate a cyclized molecule. Although Wang describes a fragment of a CD4 peptide that corresponds to a region of the receptor that binds gp120, there is no indication in Wang's disclosure that the cyclized fragment binds gp120. Wang generated a cyclized molecule so as to enhance the molecule's ability to generate an immune response. Wang incorporated the promiscuous artificial Th epitope for the same reason. Wang does not mention the use of a Gal epitope for any reason nor does Wang describe how one would incorporate a Gal epitope to a peptide, especially a cyclized peptide.

Further, one would not be motivated to combine Wang and Galili et al. because there is no indication in either reference or reasonable inference that can be made that the combination would result in the claimed composition. It is recognized that the desire of Wang and Galili et al.

is to make more potent immunogens but Galili et al. do not teach how to incorporate the Gal epitope to a peptide nor do they teach the amount of incorporation that is required to enhance immunogenicity. Galili et al. simply motivate one of skill in the art to add as many Gal epitopes as possible. As mentioned above, the techniques employed by Galili et al. also unpredictably incorporate the Gal epitope. Similarly, Wang describes a cyclized peptide but never mentions use of the Gal epitope. Although the peptide described in Wang has asparagine residues, as stated before, one would not be motivated to incorporate the Gal epitope at these sites because they exist within the CD4 binding region, Wang's desired epitope for raising antibodies. That is, there would be no motivation to combine the peptide described in Wang with the teachings of Galili et al, because the sites available for incorporation of the Gal epitope using the techniques described in Galili et al. appear within the CD4 recognition domain to which Wang desires to raise antibodies. Given the unpredictability of the techniques applied by Galili et al., the lack of knowledge with respect to the amount of Gal epitope incorporation required to enhance an immune response, the lack of knowledge with respect to the ability of the cyclized CD4 peptide to bind to gp120, and the lack of knowledge with respect to ability to incorporate the Gal epitope to amino acids that lie within a T cell epitope and maintain immunogenicity, Applicants respectfully submit that one of skill in the art would have no motivation to combine Galili et al. and Wang and would have no expectation of success at achieving the now claimed invention. Neither reference mentions or suggests synthetic conjugation of the Gal epitope to a CD4 HIV binding fragment. Neither reference mentions or suggests that the Gal epitope is synthetically conjugated to the CD4 HIV binding fragment by attachment at one amino acid. Nether reference mentions or suggests that the Gal epitope is synthetically conjugated to a hydroxylated amino acid, or an NH2 linkage, or at the N-terminus of the peptide. Accordingly, Applicants respectfully request that the obviousness rejections be withdrawn and that the now pending claims be found to be in condition for allowance.

CONCLUSION

The undersigned has made a good faith effort to respond to the Office Action and to place the claims in condition for allowance. Nevertheless, if any undeveloped issues remain or if any

issues require clarification, the Examiner is respectfully requested to call Applicants' attorney, Eric S. Furman, Ph.D. at (610) 687-8643 (direct line) to resolve such issues promptly.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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